46. (new) The kit of claim 33, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.

Please cancel claims 48, 49, 55 and 56.

REMARKS

Claims 1, 17 and 33 were amended. No new matter has been added.

Claims 8, 9, 10, 15, 24, 25, 26, 31, 37, 39, 40, 41, 42 and 46 correspond to the originally filed claims which were canceled in the Preliminary Amendment.

Support for the amendments can be found at least at pages 14 and 18, and in cancelled claim 11.

The Examiner regards the pending claims as obvious in view of the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,919,815.

The Examiner's remarks are brief, and are presented here for convenience.

> The instant invention and the patented invention bear the relationship of genus versus species. The instant composition contains polyoxyethylated castor oil which had been taught by Bradley et al., note lines 32-41, column 17 of the patent as a carrier, and a wide range of dosage is also taught by the same patent at lines 10-21, column 18. Thus, the claimed invention would be obvious over the patent invention.

Applicants respectfully request reconsideration on the following grounds.

The '815 patent discloses a broad range of doses useful for a variety of species of subjects. That range of doses does not set forth what one of ordinary skill in the art would expect the dose to be for any particular species. The MTD of a cancer drug, as is known by those of ordinary skill in the art, differs markedly from species to species.

The subjects covered by the '815 patent are: "The subject as used herein means humans, primates, horses, cows, pigs, sheep, goat, dogs, cats, and rodents". (Column 17, lines 55-60). Applicants believe that the dose ranges and formulations disclosed and claimed in the instant application are surprising and unexpected from those disclosed in the '815 patent. The dose ranges are species-specific in that the MTD is specific for the subject being treated, as now more particularly and distinctly claimed.

The surprising and unexpected findings are set forth, for example, at pages 12 and 14 of the specification. As set forth at page 12, lines 5-9, the MTD of paclitaxel in humans is 225 mg/m2. This is

well-known as paclitaxel is clinically approved and has been used in thousands of cancer patients. As set forth at page 14, the MTD of the conjugate DHA-paclitaxel is 4-5 times greater by weight in the subjects tested. This would mean a predicted dose in humans based on the present disclosure of 900-1125 mg/m2 (4-5 times 225 mg/m2). It is noted that 1125 mg/m2 is completely unexpected as a dosage for humans. Nothing in the '815 patent predicts such a stark difference from the prior art.

Since the filing of the present application, DHA-paclitaxel has completed a Phase-I clinical trial and it has been determined that the maximum tolerated dose in humans is at least 1100 mg/m2. Seven phase II clinical trials are now underway with DHA-paclitaxel at the dose of 1100 mg/m2. This is more than four times on a molar basis the amount of taxol that has been determined to be administerable to humans without problematic side-effects. Remarkably, even at this high dose, the patients do not experience hair loss and some of the other side effects characteristic of unconjugated paclitaxel. This dose simply is not predictable from the prior art.

It is noted again that the maximum tolerated doses are species-specific. The maximum tolerated dose for paclitaxel in a human is very different from that in a dog, which in turn differs from that in a rodent, and so on. The '815 patent taught a range which was appropriate for covering all species falling within the definition of subjects. At the time of the '815 invention, it was known that the maximum tolerated dose for paclitaxel in a human was 225 mg/m2. It was completely unpredictable from the '815 patent that the conjugates would be able to be dosed in a human at four times the maximum tolerated dose versus unconjugated drug in a human.

While, broadly speaking, applicants understand the genus-species analysis drawn by the Examiner, it is very clear in the present circumstances that the species of dose being claimed was not shown or suggested by the '815 patent and, in fact, is surprising and unpredictably so.

As mentioned in the prior Response and the prior Amendment of April 2000, an Examiner is not permitted to ignore unexpected results alleged and demonstrated. The controlling law was presented in that Amendment. The unexpected results are over and above the teachings of the cited '815 patent. It is believed that the Examiner has not met his burden in rejecting the present claims and that there is not a *prima facie* basis for rejecting the claims, as the unexpected results demonstrated in the present case have not been addressed by the Examiner. Applicants, respectfully request reconsideration of this point, particularly in view of the amendments to the claims, which are intended to clarify that the maximum tolerated dose is a species-specific measurement, not a single measurement which applies cross-species.

The maximum tolerated dose of numerous fatty acid-anticancer drug conjugates, according to the invention, now have been tested in rodents. Among them are camptothecin, podophyllotoxin, doxorubicin, and epothilone D. The conjugates consistently had MTDs greater than the MTD of the unconjugated drug, and in some cases, greater than six times the MTD of the unconjugated drug. Such a result, consistent with the teaching of the present invention, simply was not remotely predictable from the '815 patent. Applicants would be glad to supply a declaration to this effect if it would advance prosecution.

Applicants again point out that certain of the claims are directed to fatty acid-taxane conjugate compositions. Again, these compositions were not remotely suggested and were unpredictable from the '815 patent. The Amendment of April 11, 2000 sets forth at page 5 certain of the novel aspects of the present invention which are embraced by the independent claims. It may be convenient for the Examiner to refer to this summary. The law regarding unexpected results is presented in that same Amendment.

A surprising aspect of the invention is the ability to solubilize much higher concentrations of the conjugates of the invention in surfactants such as polyoxyethylated castor oils than is possible for anticancer compounds which are not conjugated to fatty acids. For example, applicants can routinely obtain 40 mg/ml or more of the docosahexaenoic acid-paclitaxel conjugate in a 50%/50% Cremaphor/ethanol co-solvent system, whereas the prior art typically is at 6 mg/ml of paclitaxel in the same co-solvent system.

Another surprising aspect of the invention is the ability to dissolve conjugates of taxanes and fatty acids in ethanol at very high concentrations, e.g., 100 mg/ml. The conjugates are very stable when stored in ethanol in that manner.

Another surprising aspect of the invention is the ability to administer higher concentrations of the conjugates of the invention (than the unconjugated anticancer drug) and in shorter durations. For example, currently 0.3-1.2 mg/ml of paclitaxel in 10%/10% Cremaphor/ethanol is administered over at least 3 hours. The present invention permits much higher concentrations of the fatty acid-taxane conjugates and in less than 3 hours.

The foregoing unexpected results are embraced by the rejected claims. For example, method claims 17, 21, 23, and 28 describe administering fatty acid-anticancer compound conjugates in amounts which far exceed the maximum tolerated dose for the unconjugated anticancer compounds. Claim 33 describes a kit for carrying out the method of claim 17. Claim 1 describes a formulation in a container for administration to a subject, wherein the container contains the amount of conjugate necessary for carrying

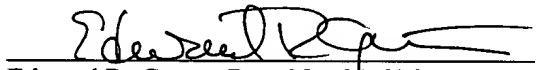
out the method described in claim 17. Other aspects of the invention are featured in other of the independent claims.

Again, these compositions were not remotely suggested and were unpredictable from the '815 patent. The Amendment of April 11, 2000 sets forth at page 5 certain of the novel aspects of the present invention which are embraced by the independent claims. It may be convenient for the Examiner to refer to this summary. The law regarding unexpected results is presented in that same Amendment.

In summary, the dose ranges and formulations and compositions claimed in the instant application are neither shown nor suggested by the prior art. For example, it simply is unpredictable from the prior art that one could administer 1100 mg/m2 of DHA-paclitaxel to a human, which is more than four times on a weight or molar basis than the MTD for paclitaxel in humans. Even more astounding, is that this is possible without the observation of the same level of dose-limiting toxicity observed with paclitaxel at one-quarter the dose. In fact, certain of the side-effects typical of administration of paclitaxel in clinical doses have been absent, such as the loss of appetite and loss of hair.

Applicants and the Examiner had arranged for an interview regarding the present case, which was canceled when airports were closed surrounding the tragic events of September 11, 2001. Applicants still would appreciate an opportunity to interview this case and request that the Examiner contact the undersigned attorney to arrange a time for having such an interview.

Respectfully submitted,



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MARKED-UP CLAIMS

1. (amended) A fatty acid-anticancer compound conjugate composition for administration to a subject, comprising at least one fatty acid-anticancer compound conjugate in a container for administration to a subject, wherein the amount of the fatty acid-anticancer compound in the container is at least about 10% on a molar basis greater than the maximum tolerated dose (MTD) in the subject for the unconjugated at least one anticancer compound, wherein the container is a container for intravenous administration.

8. (new) The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount in the container is at least about 200% greater than the MTD for the unconjugated at least one anticancer compound.

9. (new) The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount in the container is at least about 300% greater than the MTD for the unconjugated at least one anticancer compound.

10. (new) The fatty acid-anticancer compound conjugate composition of claim 1, wherein the amount in the container is at least about 400% greater than the MTD for the unconjugated at least one anticancer compound.

15. (new) The fatty acid-anticancer compound conjugate composition of claim 1, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.

17. (amended) A method for treating a subject having an abnormal mammalian cell proliferative disorder, comprising administering to the subject a fatty acid-anticancer compound conjugate composition in an amount which is at least about 10% on a molar basis greater than the maximum tolerated dose (MTD) in the subject for the unconjugated at least one anticancer compound.

24. (new) The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 200% greater than the MTD for the unconjugated at least one anticancer compound.

25. (new) The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 300% greater than the MTD for the unconjugated at least one anticancer compound.

26. (new) The method of claim 17, wherein the amount of the fatty acid-anticancer compound conjugate composition administered is at least about 400% greater than the MTD for the unconjugated at least one anticancer compound.

31. (new) The method of claim 17, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.

33. (amended) A kit for administration of a fatty acid-anticancer compound conjugate composition to a subject, comprising

a container containing at least one fatty acid-anticancer compound conjugate, and

instructions for administering the at least one fatty acid-anticancer compound conjugate to subject in need of such treatment in an amount which is at least about 10% on a molar basis greater than the maximum tolerated dose (MTD) in the subject for the unconjugated at least one anticancer compound.

37. (new) The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound conjugate is at least about 50% greater than the MTD for the unconjugated at least one anticancer compound.

39. (new) The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound conjugate is at least about 100% greater than the MTD for the unconjugated at least one anticancer compound.

40. (new) The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound conjugate is at least about 200% greater than the MTD for the unconjugated at least one anticancer compound.

41. (new) The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound conjugate is at least about 300% greater than the MTD for the unconjugated at least one anticancer compound.

42. (new) The kit of claim 33, wherein the amount of the at least one fatty acid-anticancer compound conjugate is at least about 400% greater than the MTD for the unconjugated at least one anticancer compound.

46. (new) The kit of claim 33, wherein the fatty acid is a C8-C26 unbranched, naturally occurring fatty acid.